Comprehensive DFT and MP2 Level Investigations of Reaction of 2,3-Dihydro-1,5-benzodiazepine-2-thiones with Hydrazine

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Density functional theory approach was used for the 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione compound to determine the mechanism of hydrazinolysis of 4-substituted 2,3-dihydro-1,5-benzodiazepine-2-thiones. Single-point calculations at the MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level were performed for the more accurate energy prediction. The solvent effect was taken into account by carrying out single-point calculations using the PCM methodology. The obtained results show that in the investigating mechanism the first step consists of the hydrazine molecule addition to the thiocarbonyl bond of the 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione following removal of H_2S. Further addition of another hydrazine molecule to the azomethyne bond and cyclization with pyrazole ring formation occur, and then the diazepine ring-opening and the removal of hydrazine molecule proceed. Finally, imine−enamine tautomerization leads to 5-*N*-(2-aminophenyl-1-amino)-3-phenylpyrazole as a main product that is in agreement with the experimental observation. The cyclization step is a rate-determining step of this reaction.

Introduction

The recyclization of heterocyclic compounds in reactions with hydrazine and its derivatives has been extensively studied experimentally and has been shown to be very important in organic synthesis.[1−8] Despite numerous predictions of the possible mechanisms of the recyclization processes, theoretical verification for the proposed mechanisms by quantum mechanical calculations has not been yet accomplished. In a recent paper,[9] we reported the theoretical investigation on hydrazinolysis of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2-one leading to 3-methylpyrazolone-5. To broaden our analysis of the 1,5-benzodiazepines, in this study, we investigated the mechanism of the recyclization reaction which takes place during interaction of 2,3-dihydro-1,5-benzodiazepine-2-thiones with hydrazine (Scheme 1). Chemistry of 1,5-benzodiazepine-2-thiones is a dynamically developing area that is caused by their biological activity and their applications as starting materials in the synthesis of several heterocyclic compounds for potential biological actvities.[5,10−16] Especially, attention has been directed toward recyclization and cyclofunctionalization processes of the seven-membered ring of 1,5-benzodiazepine-2-thiones that lead to formation of a new heterocyclic system. In particular, hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione (**1a**) was carried out by Doumbia et al.[5] as a first step for synthesis of new quinoxaline derivatives having potential biological interest. It was reported that 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione (**1a**) reacts with hydrazine to give 3-*N*-(2-aminophenyl-1-amino)-5-phenylpyrazole (**2a**). A similar result was also obtained by Gharbi et al.[14] for hydrazinolysis of 4-(2-hydroxyphenyl)-2,3-dihydro-1,5-benzodiazepine-2-thione (**1b**). Interestingly (depending on time of reaction), interaction of 4-adamantyl-1,5-benzodiazepin-2-thione (**1c**) with hydrazine in absolute ethanol results in formation of 2-hydrazine derivative (**3c**) and 5-*N*-(2-aminophenyl-1-amino)-3-adamantylpyrazole (**2c**).[7] The formation of compound **3c** can be explained by the steric shielding of carbon atom C_4 by the adamantyl group.

On the basis of experimental results, Essassi and Salem proposed[8] that the hydrazinolysis reaction of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione consists of hydrazine addition to thiocarbonyl group, cyclization, seven-membered ring-opening at the C_4-N_5 bond, and H_2S molecule removal (see Scheme 2). A similar mechanism was assumed also for pyrazolodiazepine-2-thiones.[6] In the present study, to clarify details of the recyclization mechanism of 2,3-dihydro-1,5-benzodiazepine-2-thiones during hydrazinolysis, the theoretical investigation of the mechanism of interaction of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione with hydrazine was carried out.

Computational Methodology

All calculations were carried out with the Gaussian 03 program package.[17] The relevant stationary points (reactant complexes, intermediates, transition states, and product complexes) were fully optimized in the gas phase using the density functional theory (DFT) method with hybrid density functional (B3LYP)[18,19] in conjunction with the 6-311+G(d,p) basis set. Stationary points were further characterized as minima with all real frequencies or as transition states with only one imaginary frequency by computations of analytic harmonic vibrational frequencies at the same theory level as geometry optimization. Gibbs free energies of activation ($\Delta G^{\ddagger}$) were calculated as the difference of free energies between transition states and prereactive complexes. The zero-point energies were scaled by a factor of 0.9877[20] recommended for the B3LYP/6-311+G(d,p)

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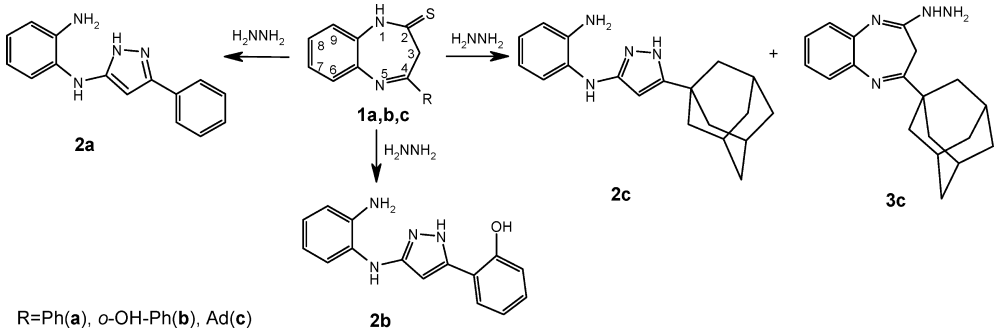
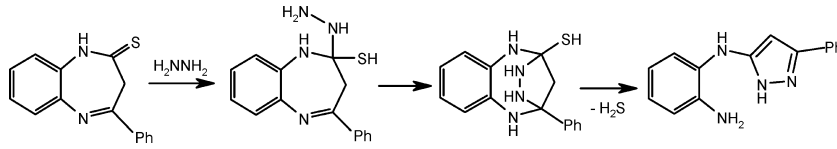
SCHEME 1



SCHEME 2



level. Single-point computations at the MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level were performed to improve evaluation of the energies of the considered species.

Specific solvation was taken into account by explicit involvement of ethanol molecules in the reaction process. In addition, solvent effects were predicted with the self-consistent reaction field (SCRF) method on the basis of the polarized continuum model (PCM).[21,22] In this work, single-point energy calculations at the PCM/MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level were carried out in ethanol solution on the basis of the gas-phase optimized geometries.

Results and Discussion

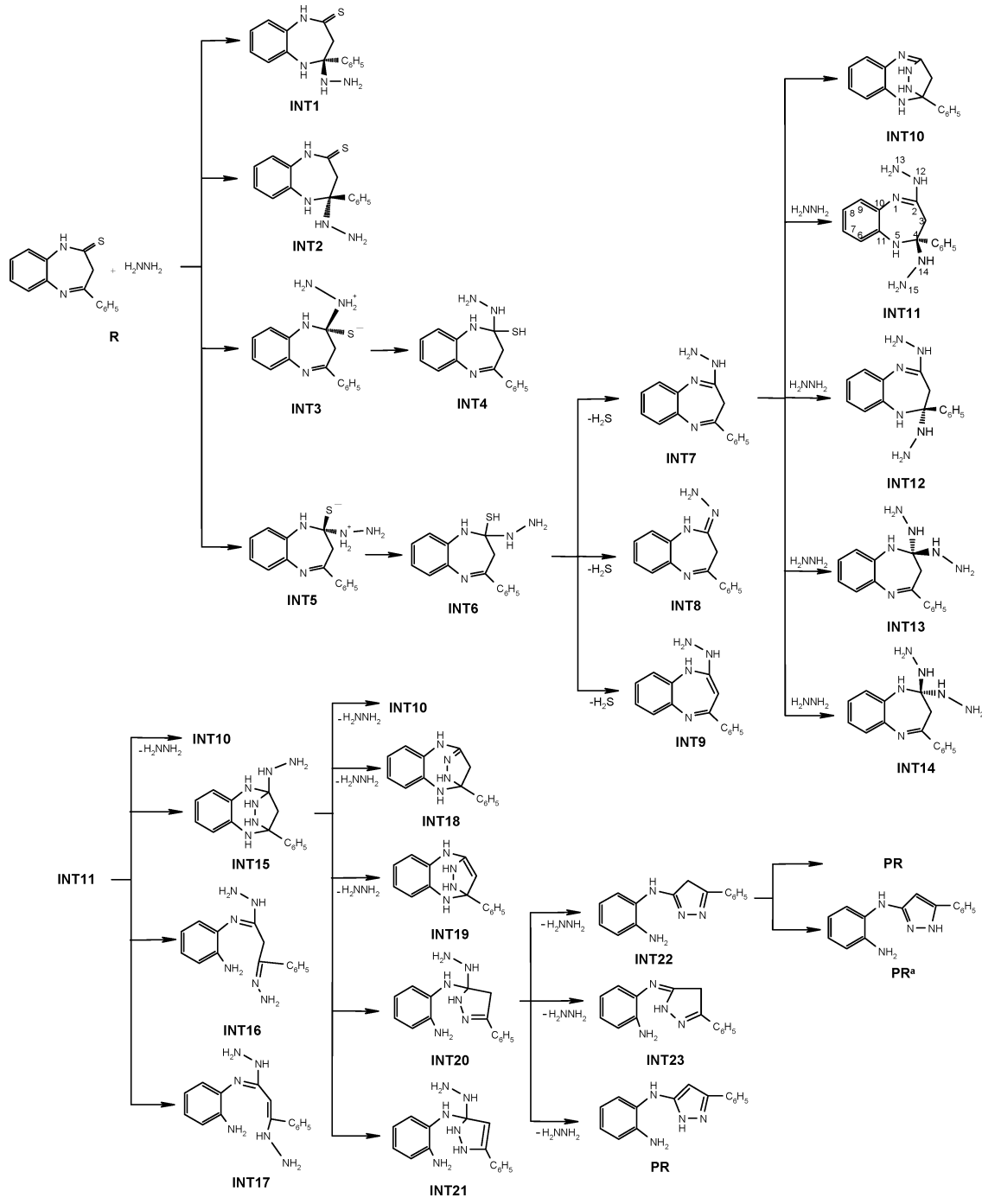
To conclusively characterize the reaction pathway, both the activation barriers (kinetic control) and the relative stability of isomeric intermediates (thermodynamic control) should be determined. There are general rules that should be taken into consideration when the mechanism of reaction is investigated. Initially, the reaction occurs through the pathway that includes the lowest barriers. Therefore, irreversible step of reaction leads to formation of a kinetic intermediate. In case of reversible reaction, there are possibilities for two directions of transformation of kinetic intermediate: (a) to thermodynamically stable intermediate and (b) to intermediate which appears on the next reaction step. This rule always applies to the reaction under kinetic control. The thermodynamic control is more important for the formation of the final reaction product.

Mechanism of 4-Phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione Hydrazinolysis. The hydrazinolysis of 2,3-dihydro-1,5-benzodiazepine-2-thiones was carried out in ethanol solution.[8] As a polar solvent, ethanol should play a very important role in stabilization of different intermediates and transition states especially in the case of proton transfer. Thus, in this study, to simulate experimental conditions, we have modeled the hydrazinolysis of thione with explicit consideration of ethanol molecule. Scheme 3 displays the reaction mechanism considered for the hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione. For simplicity, the ethanol molecules are not shown in Scheme 3. The prereactive complexes and transition states are denoted as **PRC(n_1→n_2)** and **TS(n_1→n_2)**, respectively, where n_1 is the reactant and n_2 is the product of the previous step of the reaction. The letters "et" in bold after the structure numbers refer to the presence of one molecule of ethanol. The optimized geometries of the transition states located along the reaction coordinate for ethanol-assisted hydrazinolysis are shown in Figures 1 and S1 of the Supporting Information. The relative PCM/MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) single-point energies of all structures are presented in Table 1 and are discussed throughout the text. The B3LYP/6-311+G(d,p) calculated total energies and Gibbs free energies are listed in Table S1 of the Supporting Information.

The addition of hydrazine molecule to 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione could occur by attack on the C_2 or C_4 atom. For each of these modes of attack, two stereochemically distinct pathways were considered: hydrazine approaches the electrophilic centers of thione from the same (bottom attack) or from the opposite (top attack) side of methylene group. According to the calculations, an addition of hydrazine to the C_4=N_5 bond represents a concerted process where formation of the C_4−N_{12} bond and proton transfer occur in one step. The nucleophile attachment to the C_4=N_5 bond from the opposite and from the same sites of methylene group leading to the intermediates **INT1·et** and **INT2·et** requires activation energies of 21.44 and 19.76 kcal/mol, respectively. In the case of hydrazine attack at the C_2=S bond, the reaction proceeds as a stepwise mechanism with formation of a zwitterionic intermediate during the first step. This intermediate transforms to a more stable intermediate after a fast proton transfer step. The activation energies for these steps are 15.32 and 8.54 kcal/mol, respectively, for the top attack, and they are 8.34 and 8.58 kcal/mol, respectively, in the case of the bottom attack. The obtained results indicate that the hydrazine addition to the C_2=S bond leading to **INT6·et** via a stepwise mechanism is the most energy-favorable pathway for initial interaction of hydrazine with thione (**1a**).

The elimination of the H_2S molecule presents a possible pathway for transformation of the **INT6·et** intermediate. The proton transfer from N_1, N_{12}, or C_3 atom to the SH group is needed to produce the H_2S molecule, and then it may form **INT7·et**, **INT8·et**, or **INT9·et** intermediates. It is interesting to notice that two pathways **INT6·et**→**INT7·et** and **INT6·et**→**INT8·et** are characterized by positive values of barriers in the gas phase (see Table S2), but they have negative activation energies revealed in single-point calculations (gas-phase optimized geometry) in solution (see Table 1). An appearance of negative activation barriers when solution cor-

SCHEME 3: Calculated Reaction Pathways for the Hydrazinolysis Mechanism of 4-Phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione



rection is taken into account can be explained by more efficient stabilization of transition states compared to intermediates in solution. Thus, **INT6·et** may not represent a local minimum structure in solution. Also, **INT5·et** may be transformed directly to **INT7·et** or **INT8·et.** Molecular structures **INT7·et** and **INT8·et** represent two tautomers which can easily transform into each other by a single proton transfer between N_1 and N_{12} atoms. The formation of intermediate **INT7·et** as a more stable structure compared to **INT8·et** (see Table 1) is the most favorable pathway for this step.

The nitrogen atom N_{12} at the sp^2-hybridized carbon atom C_2 is located in the $C_2-N_1-C_{10}$ plane; therefore, the amino group in **INT7·et** is spatially distant from C_4 atom and cannot attack it directly. This is confirmed by a very high activation barrier (58.15 kcal/mol) for **INT7·et→INT10·et** transformation. Therefore, a participation of another hydrazine molecule is necessary to continue the hydrazinolysis process. The addition of a second hydrazine molecule to both reaction centers C_2 and C_4 is considered as a possible way of intermediate **INT7·et** transformation. The lower activation energy (26.97 kcal/mol) corresponds to hydrazine addition to $C_4=N_5$ double bond from the opposite site of methylene group with formation of **INT11·et** intermediate. The re-examination of this stage of reaction with explicit consideration of two ethanol molecules results in reduction of the activation barrier to 23.27 kcal/mol.

The seven-membered ring-opening with cleavage of the C_4-N_5 bond and cyclization with pyrazole ring formation are discussed as possible transformation ways of intermediate

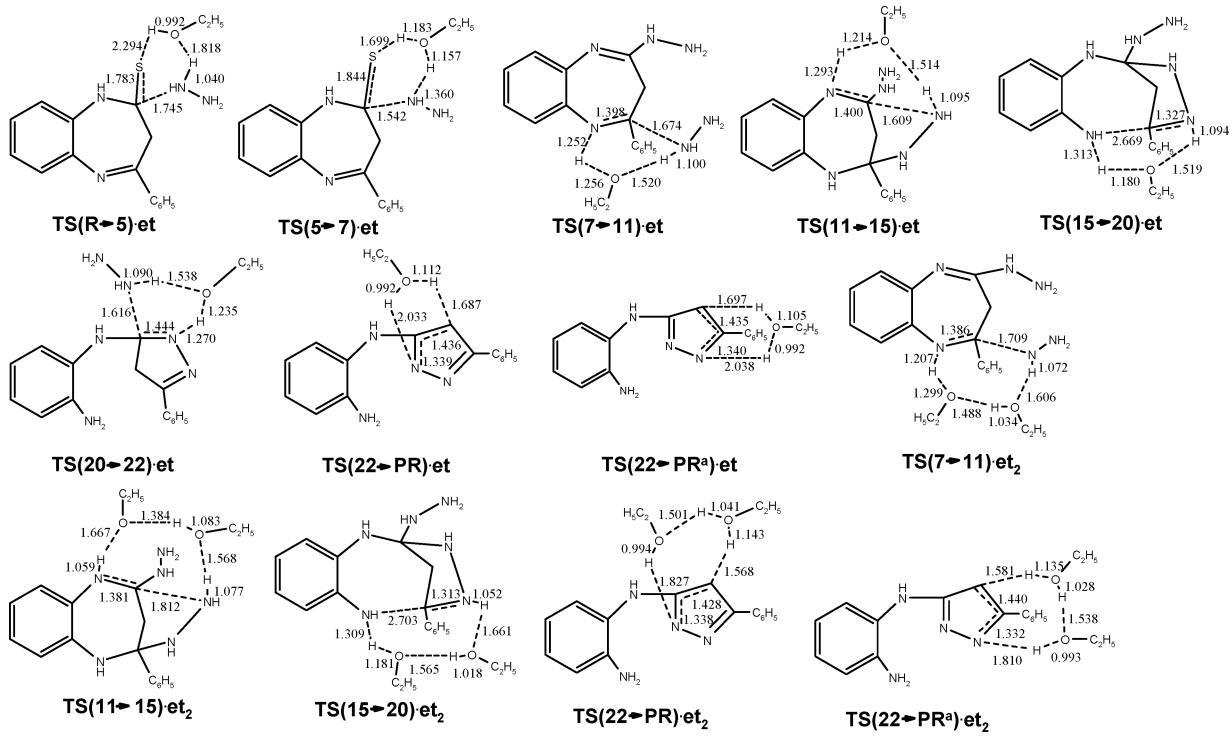


Figure 1. B3LYP/6-311+G(d,p) calculated geometric parameters of key transition state structures for ethanol-assisted 4-phenyl-2,3-dihydro-1,5-benzodiazepin-2-thione hydrazinolysis. All distances shown in the figures are in angstroms (Å).

INT11·et. As shown in Scheme 3, the cyclization (as a result of attack of the NH_2 group to the C_2 atom) could lead to intermediate **INT10·et** or **INT15·et** with activation barriers of 32.12 and 25.21 kcal/mol, respectively. The breaking of the C_4-N_5 bond is accompanied by proton transfer from N_{14} (or C_3) to N_5 and leads to formation of intermediate **INT16·et** or **INT17·et**, respectively. The activation energies for these pathways are 33.81 and 35.79 kcal/mol, respectively. Thus, the cyclization of intermediate **INT11·et** with formation of intermediate **INT15·et** is the most energetically preferable pathway. The re-examination of this stage with explicit consideration of two ethanol molecules slightly reduces the activation barrier to 25.11 kcal/mol.

The elimination of the hydrazine molecule or the opening of the seven-membered ring is possible as further transformation of the **INT15·et** intermediate. A proton transfer in intermediate **INT15·et** from the N_1, N_{15}, or C_3 to N_{12} causes consecutive departure of the hydrazine molecule, and, in addition, as the proton is abstracted, a double $N_1=C_2$, $C_2=N_{15}$, or $C_2=C_3$ bond is formed on the ring leading to **INT10·et**, **INT18·et**, or **INT19·et** intermediates. The obtained results show that these pathways are very endothermic leading to intermediates which are more than 20 kcal/mol less stable than the **INT15·et** intermediate.

The cleavage of the seven-membered ring in intermediate **INT15·et** may occur by breaking of the C_4-N_5 bond, which is accompanied by a proton transfer from N_{14} (or C_3) to N_5 and which leads to intermediate **INT20·et** or **INT21·et**. The first pathway is more preferable since it is exothermic and requires an activation energy of 28.73 kcal/mol, while for **INT15·et→INT21·et** transformation, additional energy of 43.20 kcal/mol is needed. As can be seen from Table 1, the transformation **INT15·et→INT20·et** is the most favorable pathway for this step.

The elimination of hydrazine molecule from intermediate **INT20·et** occurs through breaking of the N_1-C_2 bond accompanied by a proton transfer from N_{15}, N_1 or C_3 to N_{12}. The

TABLE 1: PCM/MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) Relative Gibbs Free Energies (at 298 K) for Transition States, Intermediates, and Products for Ethanol-Assisted Hydrazinolysis of 4-Phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione (kcal/mol)[a]

structure	ΔG_{rel}	structure	ΔG_{rel}
TS(R→1)·et	21.44	**TS(11→17)·et**	35.79
INT1·et	−3.23	**(INT17)·et**	32.03
TS(R→2)·et	19.76	**TS(15→10)·et**	23.77
INT2·et	1.92	**(INT10+H_2NNH_2)·et**	25.33
TS(R→3)·et	15.32	**TS(15→18)·et**	31.05
INT3·et	8.10	**(INT18+H_2NNH_2)·et**	21.02
TS(3→4)·et	8.54	**TS(15→19)·et**	58.76
INT4·et	−1.44	**(INT19+H_2NNH_2)·et**	46.85
TS(R→5)·et	8.34	**TS(15→20)·et**	28.73
INT5·et	8.17	**INT20·et**	−7.94
TS(5→6)·et	8.58	**TS(15→21)·et**	43.20
INT6·et	1.04	**INT21·et**	7.03
TS(6→7)·et	−3.26	**TS(20→22)·et**	20.00
(INT7+H_2S)·et	−7.88	**(INT22+H_2NNH_2)·et**	0.73
TS(6→8)·et	−1.49	**TS(20→23)·et**	21.43
(INT8+H_2S)·et	−4.15	**(INT23+H_2NNH_2)·et**	−0.21
TS(6→9)·et	24.57	**TS(20→PR)·et**	35.07
(INT9+H_2S)·et	1.45	**(PR+H_2NNH_2)·et**	−8.50
TS(7→10)·et	58.15	**TS(22→PR)·et**	22.37
INT10·et	33.89	**PR·et**	−11.16
TS(7→11)·et	26.97	**TS(22→PR^a)·et**	23.84
INT11·et	0.74	**PR^a·et**	−14.38
TS(7→12)·et	32.34	**TS(7→11)·et$_2$**	23.27
INT12·et	0.13	**INT11·et$_2$**	1.16
TS(7→13)·et	31.82	**TS(11→15)·et$_2$**	25.11
INT13·et	6.99	**INT15·et$_2$**	4.19
TS(7→14)·et	31.87	**TS(15→20)·et$_2$**	21.05
INT14·et	5.43	**INT20·et$_2$**	−9.48
TS(11→10)·et	32.12	**TS(22→PR)·et$_2$**	13.56
TS(11→15)·et	25.21	**PR·et$_2$**	−12.37
INT15·et	5.18	**TS(22→PR^a)·et$_2$**	13.46
TS(11→16)·et	33.81	**PR^a·et$_2$**	−12.66
(INT16)·et	−3.73		

[a] Relative to corresponding prereactive complexes.

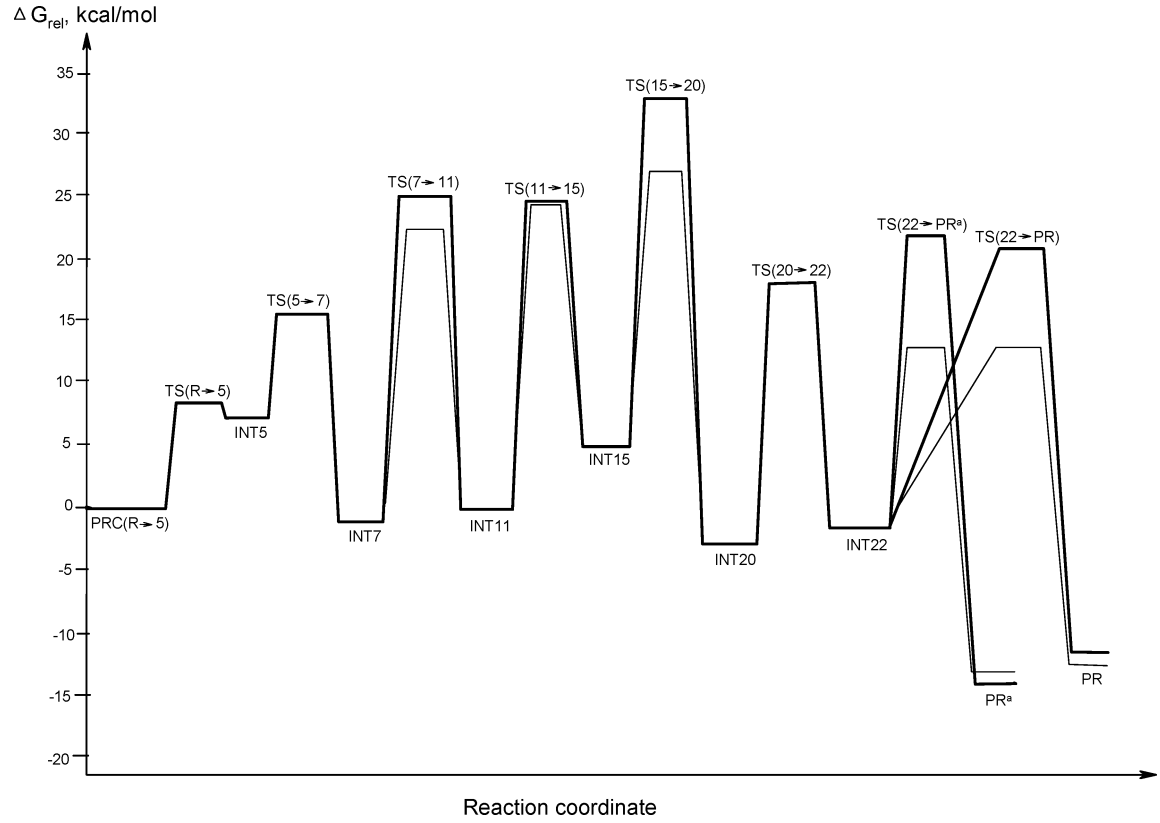


Figure 2. Relative energy profiles (kcal/mol) for ethanol-assisted hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione calculated at the PCM/MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level for one-ethanol-assisted case (solid line) and for two-ethanol-assisted case (dashed line).

first pathway leading to intermediate **INT22·et** is more preferable with an activation energy of 20.00 kcal/mol. The isomerization of the intermediate **INT22·et** by proton transfer from C_3 to N_{15} (or N_{14}) leads to formation of **PR·et** or **PR^a·et**. Molecular structures **PR** and **PR^a** represent two tautomers which can easily transform into each other by proton transfer between N_{14} and N_{15} atoms. As can be seen from Table 1, the transformation **INT22·et→PR·et** requires lower activation energy (by 1.47 kcal/mol) than the **INT22·et→PR^a·et** transformation, while the **PR·et** is 3.22 kcal/mol less stable than the **PR^a·et**. The re-examination of these pathways of reaction with explicit consideration of two ethanol molecules results in reduction of the activation barriers to 13.56 and 13.46 kcal/mol for **INT22·et$_2$→PR^a·et$_2$** and **INT22·et$_2$→PR·et$_2$** transformations, respectively. As can be seen, the activation barriers for these pathways differ insignificantly (0.10 kcal/mol). In addition, the **PR·et$_2$** is slightly less stable than **PR^a·et$_2$** (see Table 1). Thus, both these processes can occur simultaneously with preferable formation of **PR^a·et$_2$** as the main product.

On the basis of the present results, one may conclude that the energy-favorable pathway for the hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione proceeds via seven steps and that the reactive channel is represented by **R→INT5→INT7→INT11→INT15→INT20→INT22→PR+PR^a** (see Scheme 3). The cyclization leading to pyrazole ring formation is a rate-determining step for this reaction with an energy barrier of 25.11 kcal/mol using two ethanol molecules as a catalyst. The calculated potential free energy profile for the reactive channel at the PCM/MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level is presented in Figure 2.

Comparing Hydrazinolysis Mechanisms of 2,3-Dihydro-1,5-benzodiazepine-2-thiones and 2,3-Dihydro-1,5-benzodiazepin-2-ones. In our previous study,[9] it was shown that the most favorable pathway for the first step of hydrazinolysis of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2-one is the hydrazine addition to the C_4=N_5 bond. The free-energy barrier for this stage is 16.75 kcal/mol at the MP2/6-311+G(d,p)//B3LYP/6-31G(d) level. This is about 5 kcal/mol lower compared to the barrier for hydrazine addition to the C_2=O bond. The results on investigation of hydrazinolysis mechanism of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione obtained in the present study suggest the primary hydrazine attack on the C_2=S bond of thione (**1a**). This stage is 4 kcal/mol more favorable than the alternative hydrazine attack on the C_4=N_5 bond (see Table 1). Free-energy barriers for hydrazine addition to the C_4=N_5 bond of the benzodiazepine system in both mechanisms are close, while nucleophile addition to the C_2=S bond requires only half the amount of free energy necessary for an addition to the C_2=O bond. This is not surprising because higher reactivity of the thiocarbonyl bond toward the nucleophilic reagents (compared to carbonyl bond) is widely known (see, for example, review of Castro[23]).

When comparing pathways with the breaking of C−N and C−O bonds, it was noticed[9] that the C−N bond breaks easier than the C−O bond and that the leaving NH_2Ar group is more stable than the water molecule. In contrast, the C−S bond cleavage occurs more easily compared to the C−N bond rupture (see Scheme 3 and Table 1); in addition, H_2S is a good leaving group.

Thus, one can conclude that the reasons for different reaction pathways of hydrazinolysis of 2,3-dihydro-1,5-benzodiazepine-2-thiones and 2,3-dihydro-1,5-benzodiazepin-2-ones are the regiochemistry of the first reaction step and the ability to cleavage the C−O, C−N, and C−S bonds.

Conclusions

The first detailed theoretical analysis of the hydrazinolysis mechanism of 2,3-dihydro-1,5-benzodiazepine-2-thiones in etha-

nol solution is reported for 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione. All of the investigated reaction pathways indicate that the 5-*N*-(2-aminophenyl-1-amino)-3-phenylpyrazole is the main product for this reaction, which is in agreement with the experimental results for 1,5-benzodiazepine-2-thiones.[8] On the basis of computational data, the rearrangement can be described as a consecutive seven-step reaction. At the first step, the hydrazine attaches to the C_2═S bond from the same side of the methylene bridge with formation of **INT5**, which easily transforms to the **INT7** with elimination of the H_2S molecule. The second hydrazine molecule attaches to the C_4═N_5 bond from the opposite site of the methylene bridge forming **INT11**. Its further cyclization with pyrazole ring formation leads to **INT15**. The proton transfer from N_{14} to N_5 in **INT15** is accompanied by seven-membered ring-opening with cleavage of the C_4−N_5 bond. This yields **INT20**, and elimination of hydrazine molecule from this intermediate leads to the **INT22**. The isomerization of **INT22** to **PR**[a] and **PR** proceeds by proton transfer from C_3 to N_{15} and N_{14}, respectively. The energy barrier of the rate-determining step (cyclization) amounts to 25.11 kcal/mol with explicit consideration of two ethanol molecules as a catalyst.

The proposed mechanism can be useful for investigation of interaction of bifunctional nucleophiles with compounds containing the 1,5-diazepine system.

The difference in hydrazinolysis mechanisms of 2,3-dihydro-1,5-benzodiazepine-2-thiones and 2,3-dihydro-1,5-benzodiazepin-2-ones was explained on the regiochemistry of the first reaction step and the ability to cleavage the C−O, C−N, and C−S bonds.

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Supporting Information Available: The B3LYP/6-311+G(d,p) calculated total energies and Gibbs free energies tabulated for all related compounds (Table S1); the MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) calculated relative Gibbs free energies for transition states, intermediates, and product for ethanol-assisted hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione (Table S2); and the optimized geometries of the transition states located along the reaction coordinate for ethanol-assisted hydrazinolysis of 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-thione (Figure S1) are presented. This information is available free of charge via the Internet at http://pubs.acs.org.

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